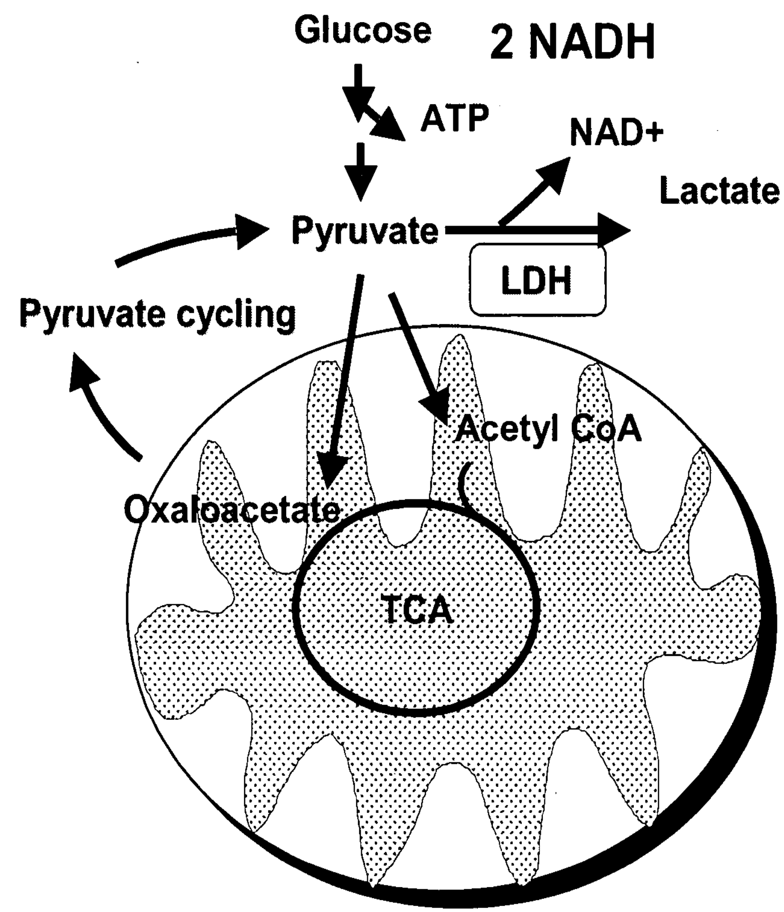


Glucose
2 NADH
ATP
NAD+
Lactate
Pyruvate
LDH
Pyruvate cycling
Acetyl CoA
Oxaloacetate
TCA

Fig. 1

GTGTGCTGGA GCCACTGTCG CCGATCTCGC GCACGCTACT GCTGCTGCTC GCCCGTCGT C CCCCATCGTG CACTAAGCGG
TCCCAAAAGA TTCAAAGTCC AAG**ATG**GCAG CCCTCAAGGA CCAGCTGATT GTGAATCTTC TTAAGGAAGA ACAGGTCCCC
CAGAACAAGA TTACAGTTGT TGGGGTTGGT GCTGTTGGCA TGGCTTGTGC CATCAGTAT C TTAATGAAGG ACTTGGCTGA
TGAGCTTGCC CTTGTTGATG TCATAGAAGA TAAGCTAAAG GGAGAGATGA TGGATCTTC A GCATGGCAGC CTTTTCCTTA
AGACACCAAA AATTGTCTCC AGCAAAGATT ATAGTGTGAC TGCAAACTCC AAGCTGGTC A TTATCACCGC GGGGGCCCGT
CAGCAAGAGG GAGAGAGCCG GCTCAATTTG GTCCAGCGAA ACGTGAACAT CTTCAAGTT C ATCATTCCAA ATGTTGTGAA
ATACAGTCCA CAGTGCAAAC TGCTCATCGT CTCAAACCCA GTGGATATCT TGACCTACG T GGCTTGGAAG ATCAGCGGCT
TCCCCAAAAA CAGAGTTATT GGAAGTGGTT GCAATCTGGA TTCGGCTCGG TTCCGTTAC C TGATGGGAGA AAGGCTGGGA
GTTCATCCAC TGAGCTGTCA CGGGTGGGTC CTGGGAGAGC ATGGCGACTC CAGTGTGCC T GTGTGGAGTG GTGTGAACGT
CGCCGGCGTC TCCCTGAAGT CTCTGAACCC GCAGCTGGGC ACGGATGCAG ACAAGGAGC A GTGGAAGGAT GTGCACAAGC
AGGTGGTTGA CAGTGCATAC GAAGTGATCA AGCTGAAAGG TTACACATCC TGGGCCATT G GCCTCTCCGT GGCAGACTTG
GCCGAGAGCA TAATGAAGAA CCTTAGGCGG GTGCATCCCA TTTCCACCAT GATTAAGGG T CTCTATGGAA TCAAGGAGGA
TGTCTTCCTC AGCGTCCCAT GTATCCTGGG ACAAAATGGA ATCTCAGATG TTGTGAAGG T GACACTGACT CCTGACGAGG
AGGCCCGCCT GAAGAAGAGT GCAGATACCC TCTGGGGAAT CCAGAAGGAG CTGCAGTTC **T** **AA**AGTCTTCC CAGTGTCCTA
GCACTTCACT GTCCAGGCTG CAGCAGGGTT TCTATGGAGA CCACGCACTT CTCATCTGA G CTGTGGTTAG TCCAGTTGGT
CCAGTTGTGT TGAGGTGGTC TGGGGGAAAT CTCAGTTCCA CAGCTCTACC CTGCTAAGT G GTACTTGTGT AGTGGTAACC
TGGTTAGTGT GACAATCCCA CTGTCTCCAA GACACACTGC CAACTGCATG CAGGCTTTG A TTACCCTGTG AGCCTGCTGC
ATTGCTGTGC TACGCACCCT CACCAAACAT GCCTAGGCCA TGAGTTCCCA GTTAGTTAT A AGCTGGCTCC AGTGTGTAAG
TCCATCGTGT ATATCTTGTG CATAAATGTT CTACAGGATA TTTTCTGTAT TATATGTGT C TGTAGTGTAC ATTGCAATAT
TACGTGAAAT GTAAGATCTG CATATGGATG ATGGAACCAA CCACTCAAGT GTCATGCCA A GGAAAACACC AAATAAACCT
TGAACAGTG

Fig. 2A

MAALKDQLIVNLLKEEQVPQNKITVVGVGAVGMACAISILMKDLADELALVDVIEDKLKGEMMDL
QHGSLFLKTPKIVSSKDYSVTANSKLVIITAGARQQEGESRLNLVQRNVNIFKFIIPNVVKYSPQ
CKLLIVSNPVDILTYVAWKISGFPKNRVIGSGCNLDSARFRYLMGERLGVHPLSCHGWVLGEHGD
SSVPVWSGVNVAGVSLKSLNPQLGTDADKEQWKDVHKQVVDSAYEVIKLKGYTSWAIGLSVADLA
ESIMKNLRRVHPISTMIKGLYGIKEDVFLSVPCILGQNGISDVVKVTLTPDEEARLKKSADTLWG
IQKELQF

Fig. 2B

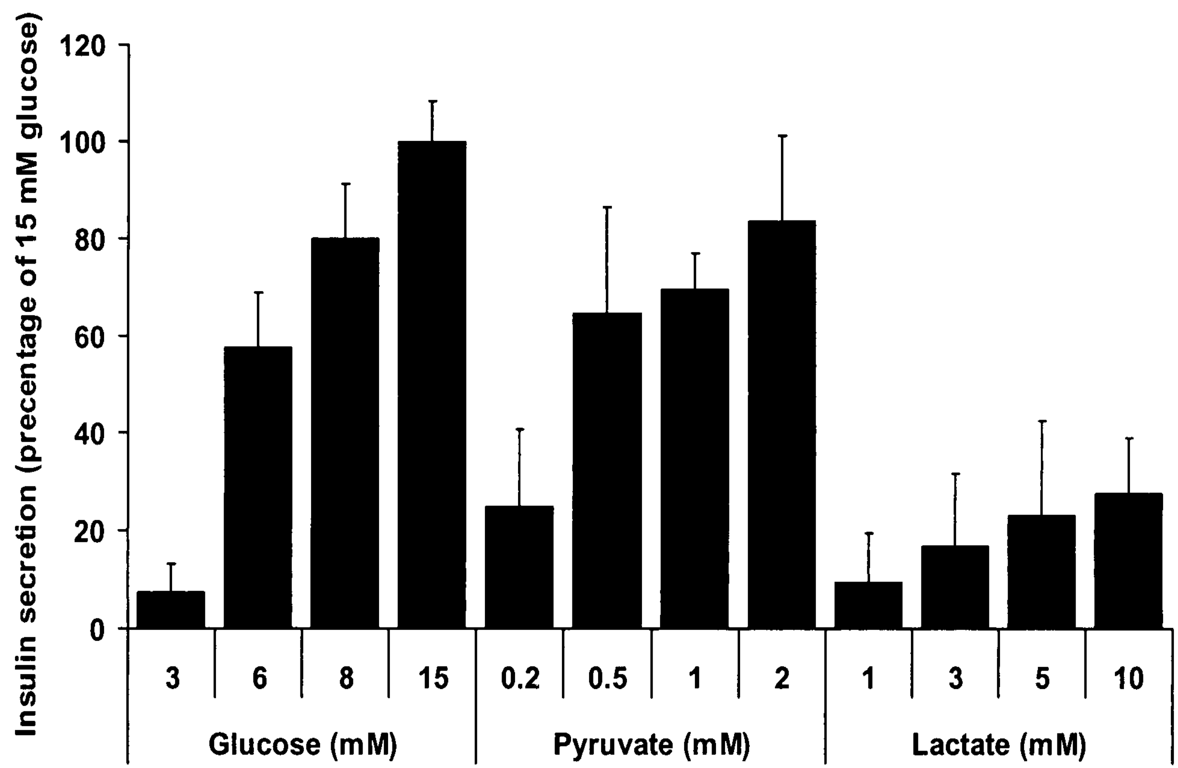

Insulin secretion (precentage of 15 mM glucose)
120
100
80
60
40
20
0
3
6
8
15
0.2
0.5
1
2
1
3
5
10
Glucose (mM)
Pyruvate (mM)
Lactate (mM)

Fig. 3

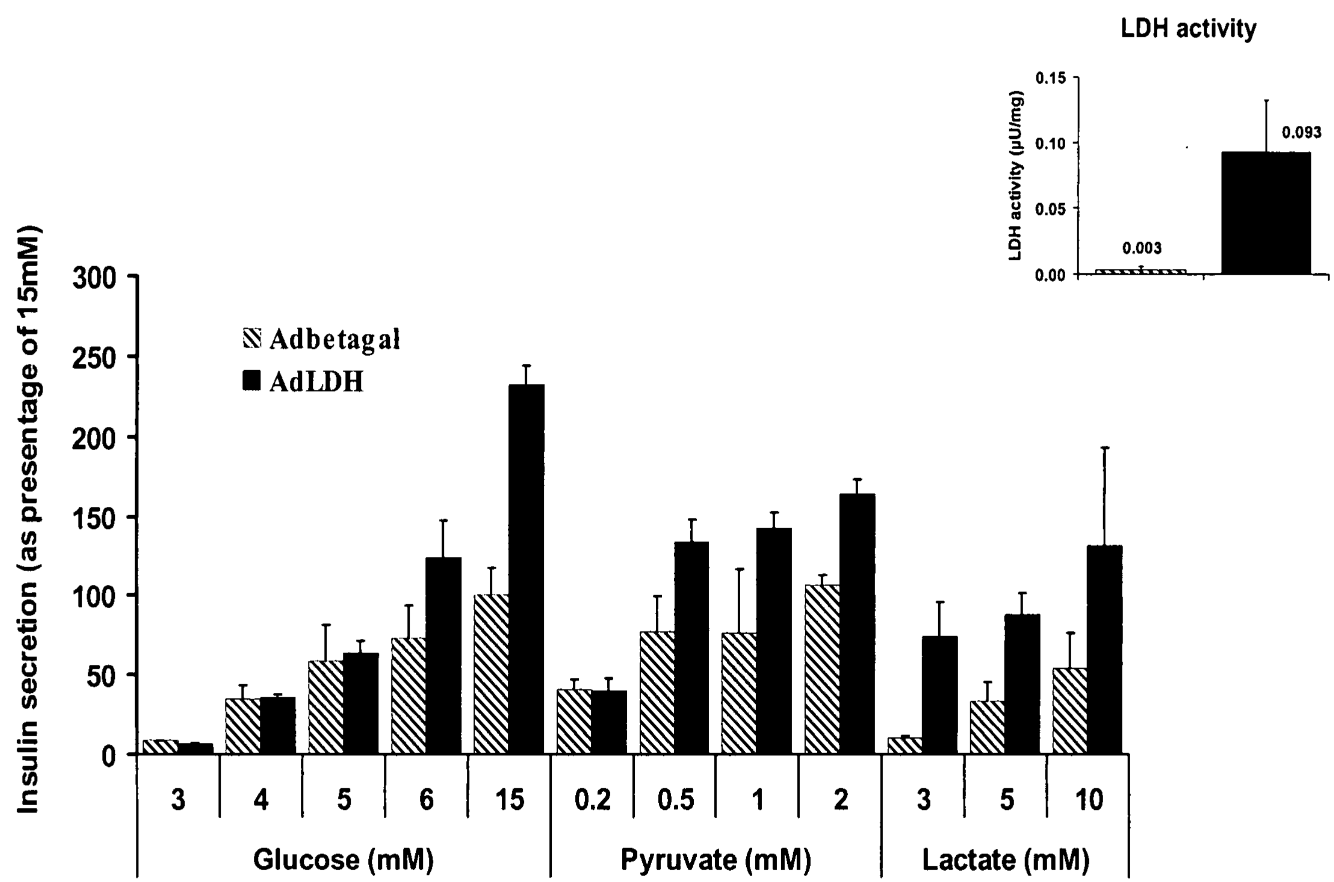

LDH activity
LDH activity (µU/mg)
0.15
0.10
0.05
0.00
0.003
0.093
Insulin secretion (as presentage of 15mM)
300
250
200
150
100
50
0
Adbetagal
AdLDH
3
4
5
6
15
0.2
0.5
1
2
3
5
10
Glucose (mM)
Pyruvate (mM)
Lactate (mM)

Fig. 4

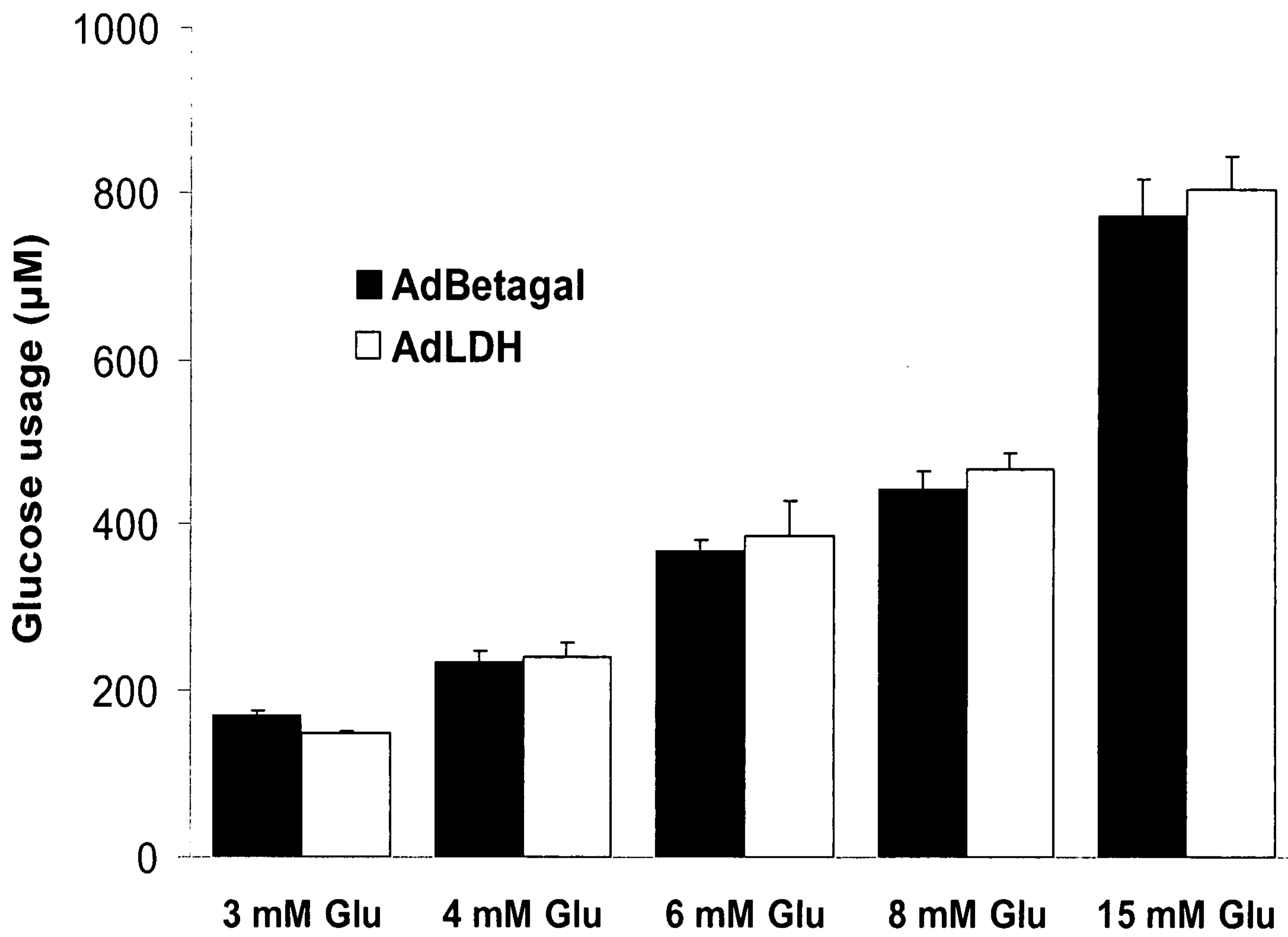
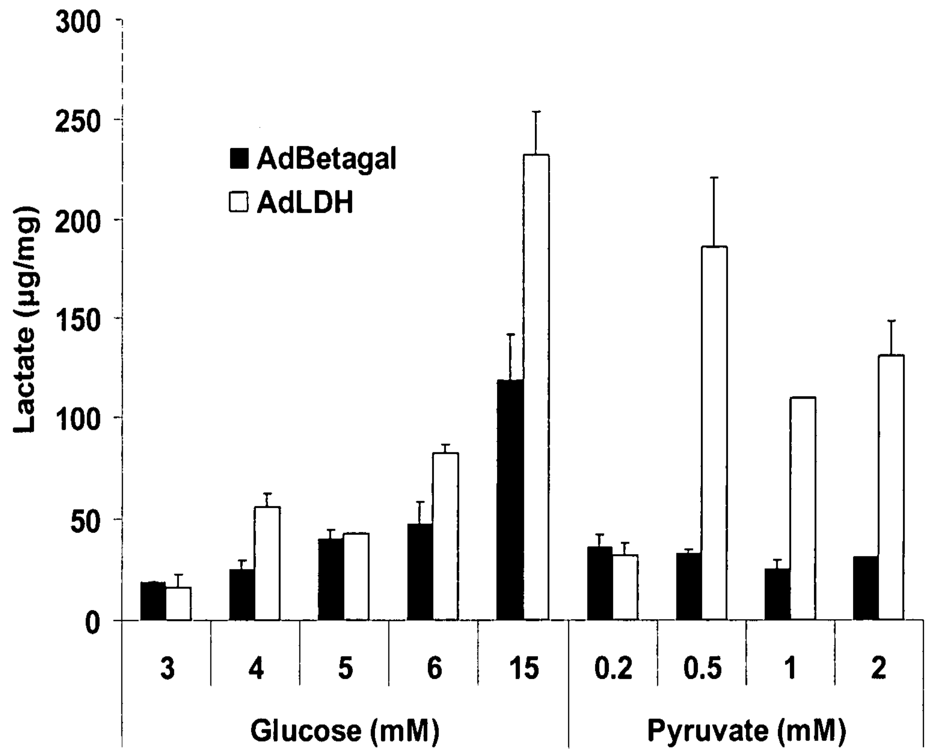

1000
800
600
400
200
0
Glucose usage (µM)
AdBetagal
AdLDH
3 mM Glu
4 mM Glu
6 mM Glu
8 mM Glu
15 mM Glu

Fig. 5



300
250
200
150
100
50
0
Lactate (µg/mg)
AdBetagal
AdLDH
3
4
5
6
15
0.2
0.5
1
2
Glucose (mM)
Pyruvate (mM)

Fig. 6

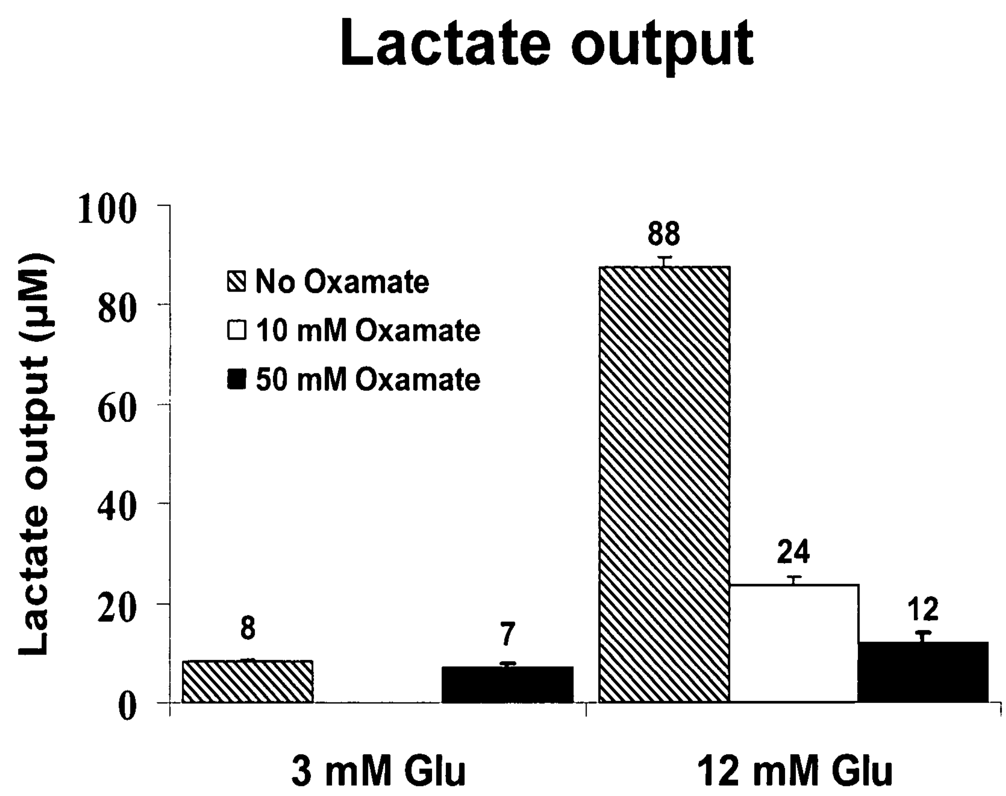

Lactate output
Lactate output (µM)
100
80
60
40
20
0
No Oxamate
10 mM Oxamate
50 mM Oxamate
8
7
88
24
12
3 mM Glu
12 mM Glu

Fig. 7A

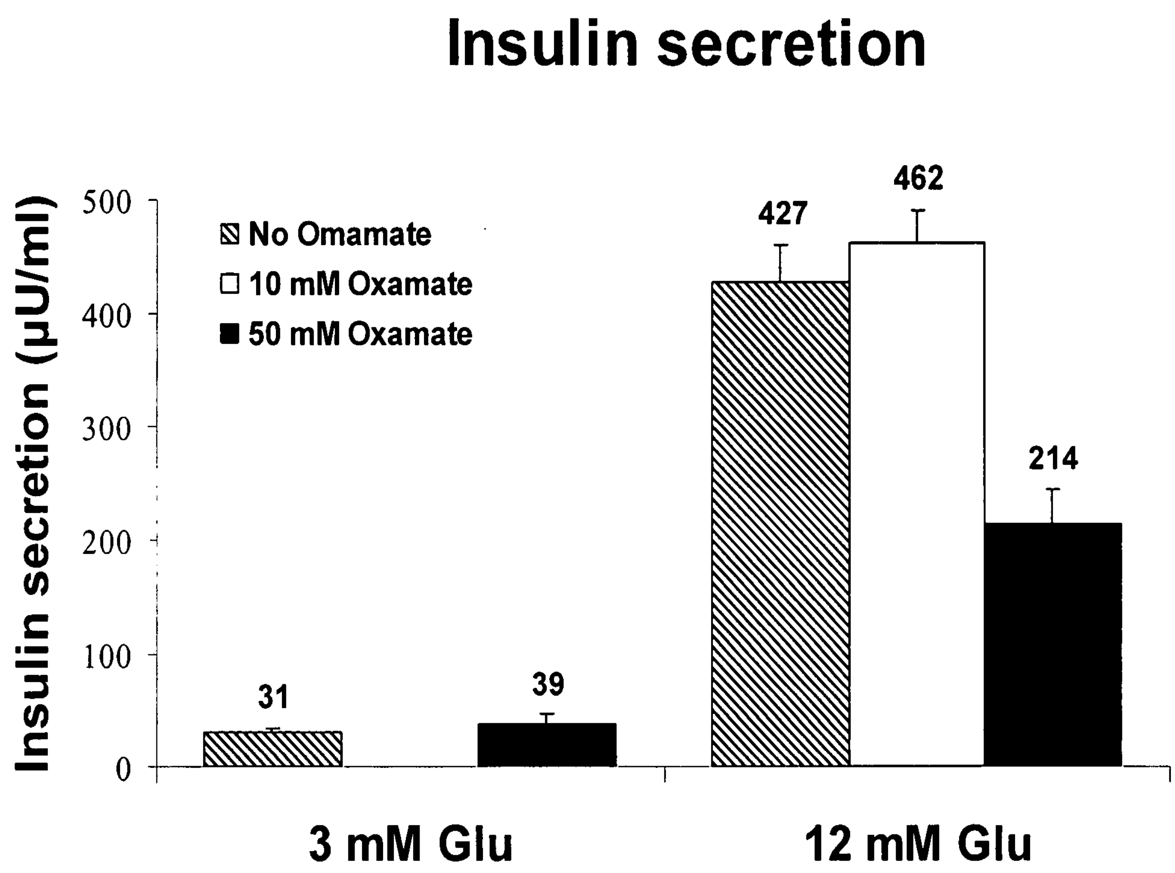

Insulin secretion
Insulin secretion (µU/ml)
500
400
300
200
100
0
No Omamate
10 mM Oxamate
50 mM Oxamate
31
39
427
462
214
3 mM Glu
12 mM Glu

Fig. 7B

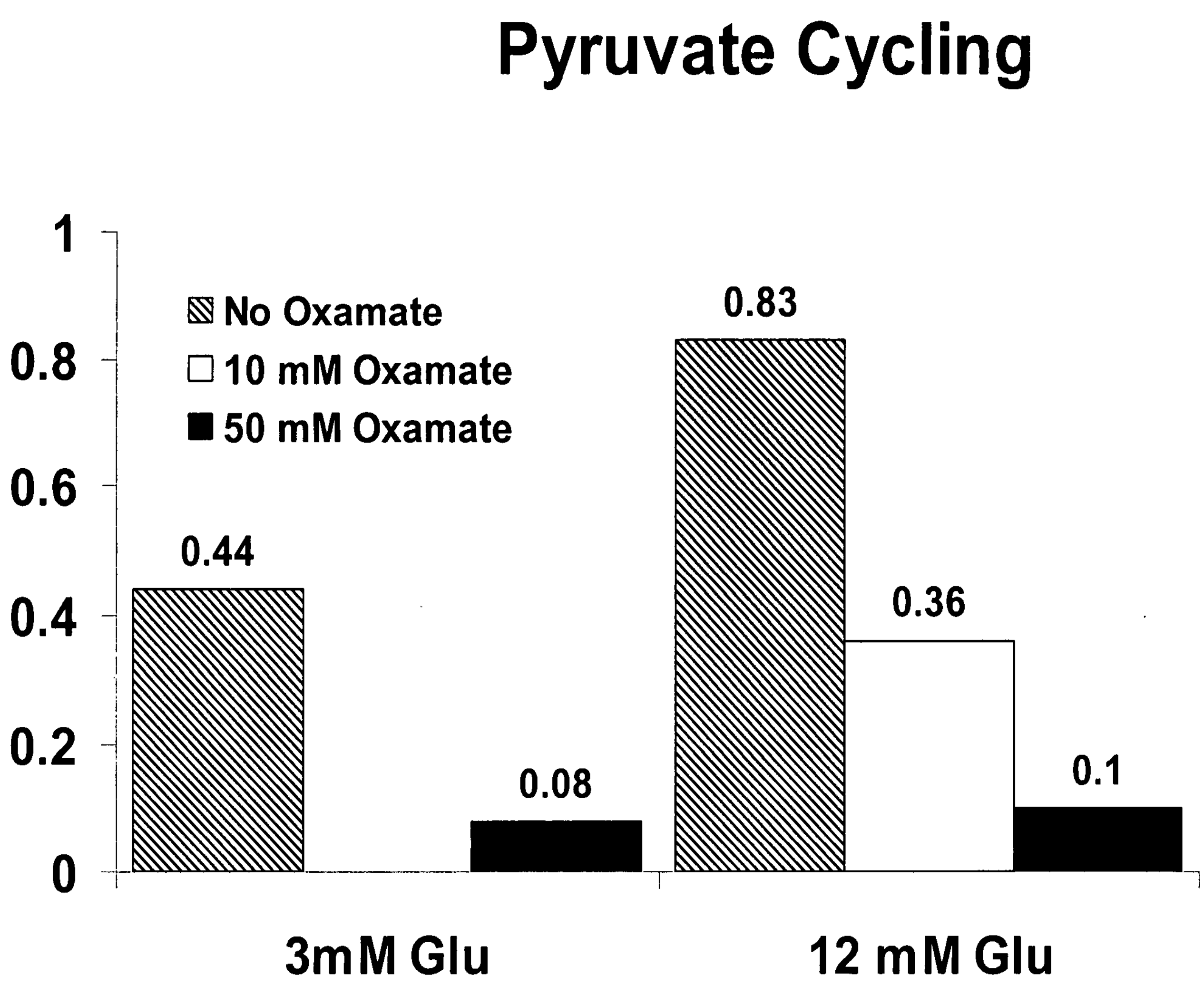

Pyruvate Cycling
1
0.8
0.6
0.4
0.2
0
No Oxamate
10 mM Oxamate
50 mM Oxamate
0.44
0.08
0.83
0.36
0.1
3mM Glu
12 mM Glu

Fig. 7C

Oxamate inhibits Insulin secretion in islets

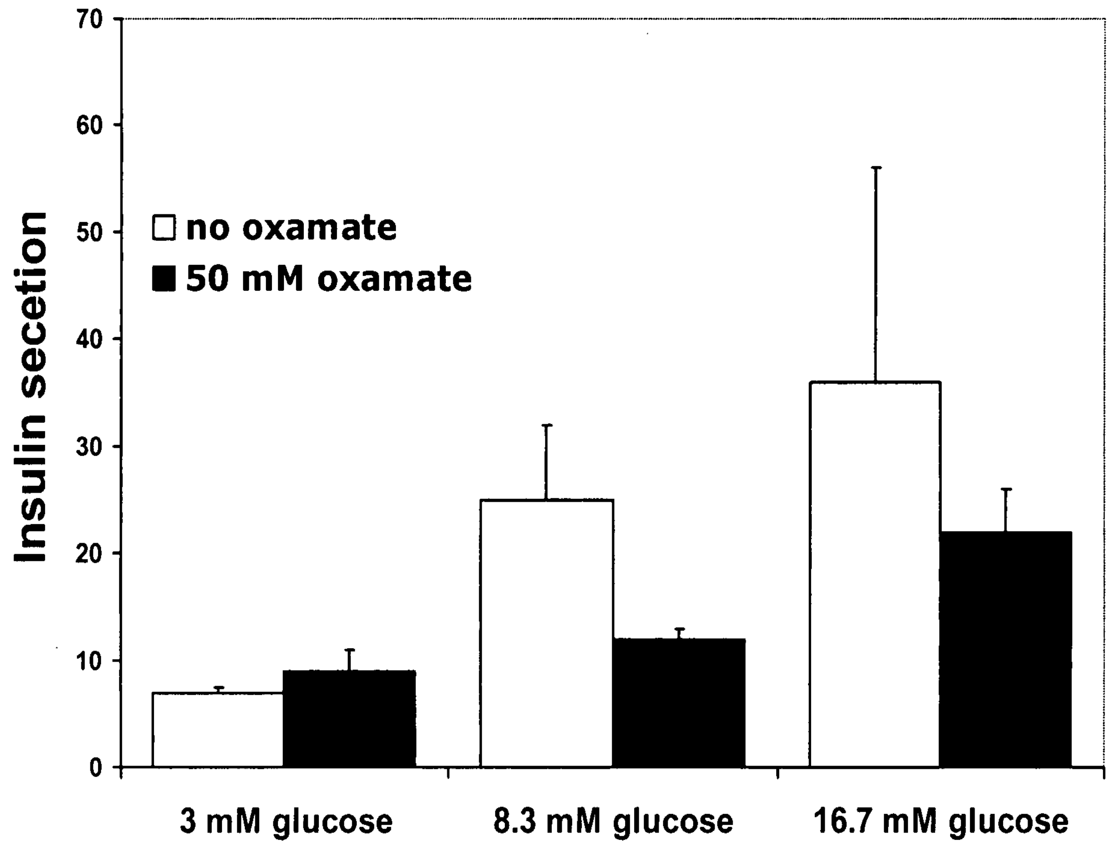


Fig. 7D

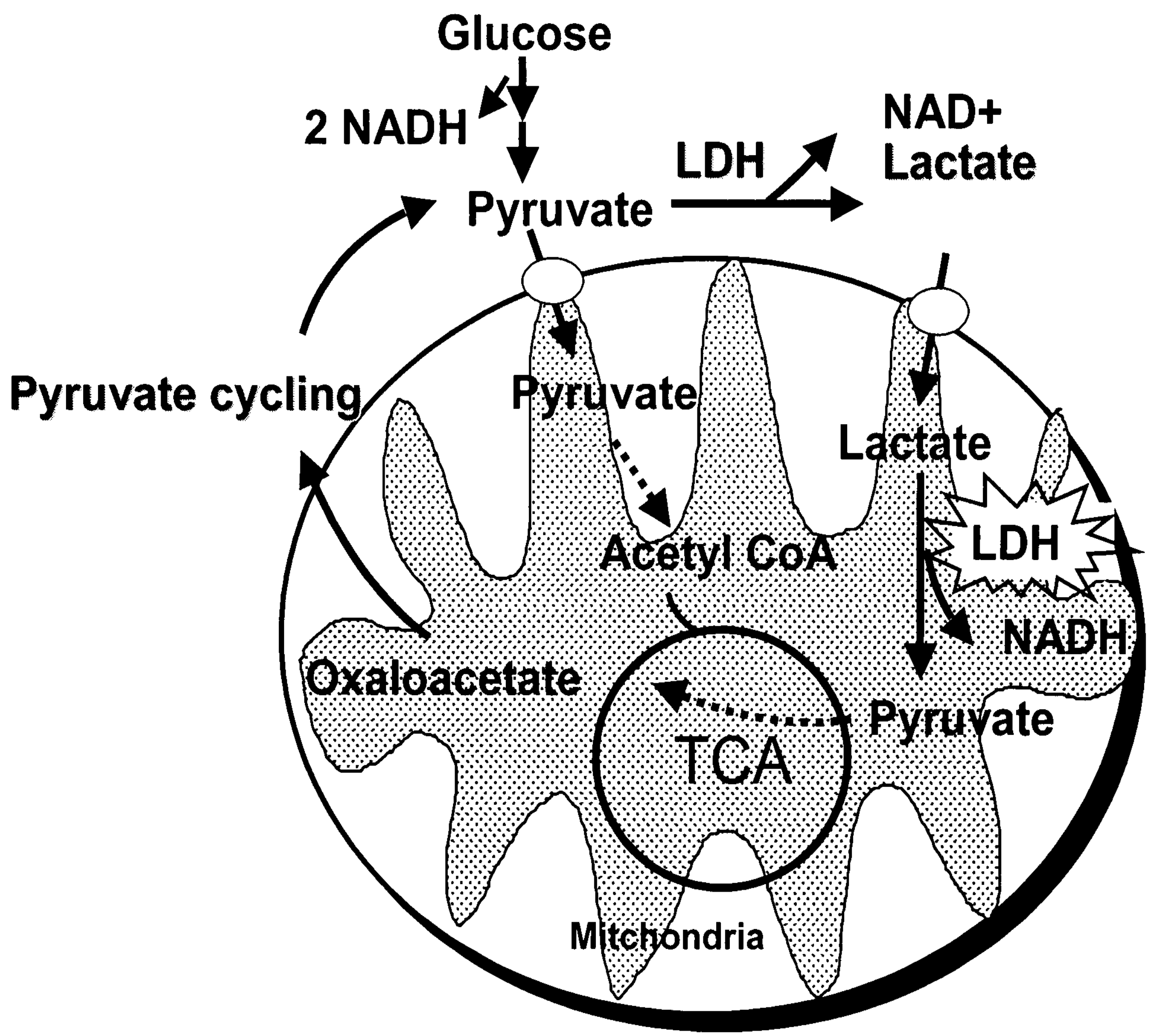

Glucose
2 NADH
Pyruvate
LDH
NAD+
Lactate
Pyruvate cycling
Pyruvate
Lactate
LDH
Acetyl CoA
NADH
Oxaloacetate
Pyruvate
TCA
Mitchondria

Fig. 8

Pyruvate Cycling Correlates with Lactate Production in Glycerol Kinase Expressing Cells.

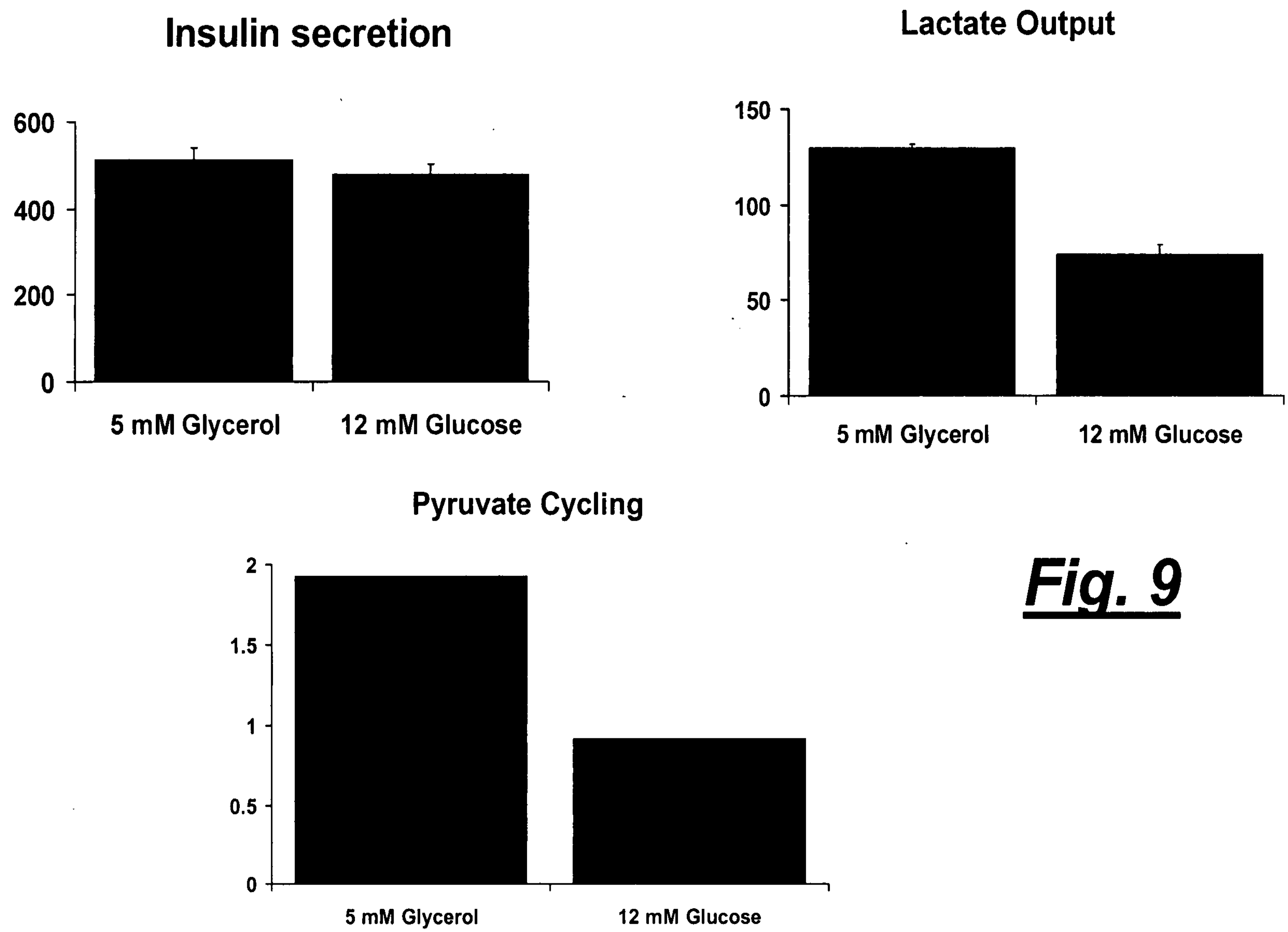
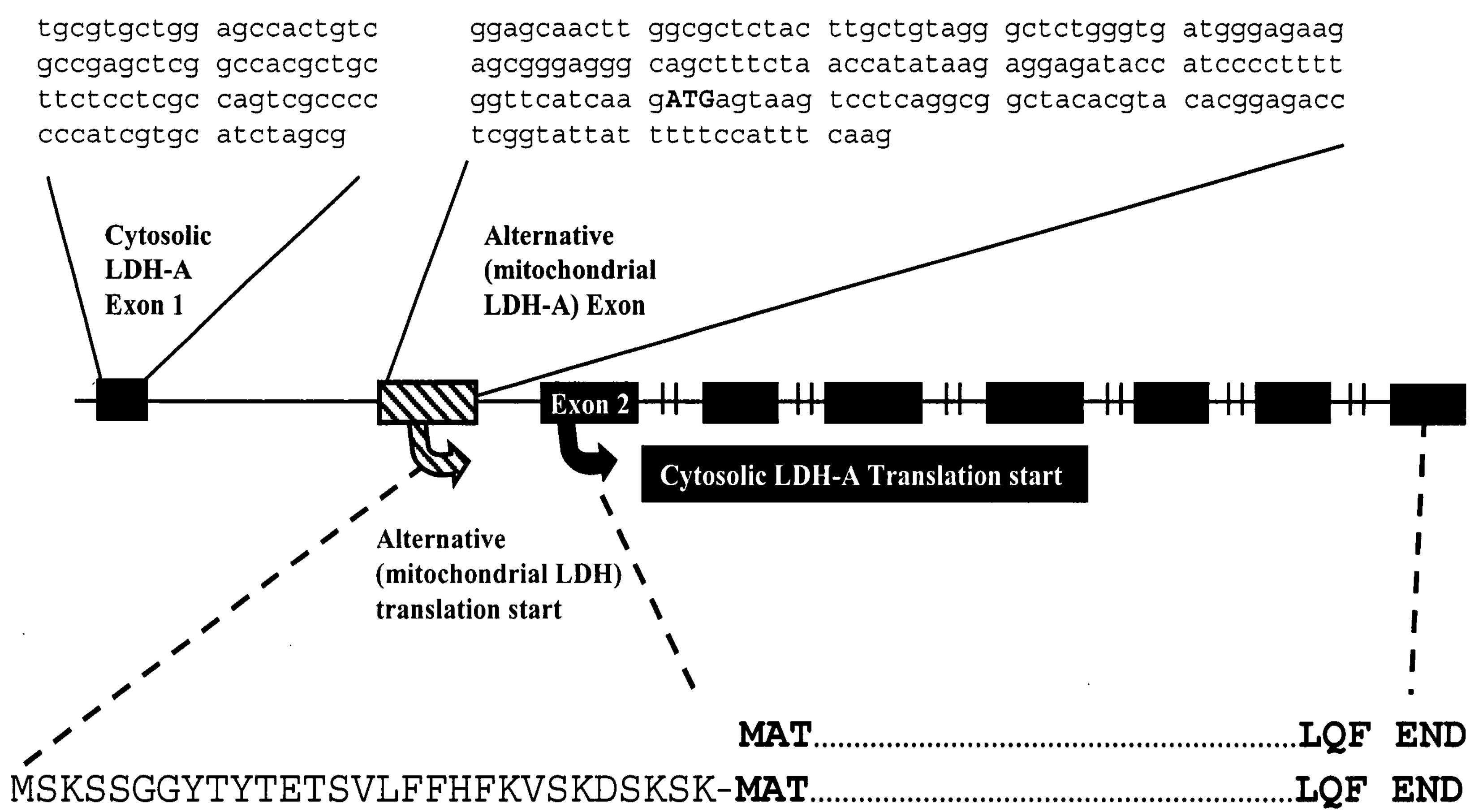


Fig. 9



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cccatcgtgc atctagcg
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agcgggaggg cagctttcta accatataag aggagatacc atcccctttt
ggttcatcaa gATGagtaag tcctcaggcg gctacacgta cacggagacc
tcggtattat ttttccattt caag
Cytosolic LDH-A Exon 1
Alternative (mitochondrial LDH-A) Exon
Exon 2
Cytosolic LDH-A Translation start
Alternative (mitochondrial LDH) translation start
MAT........LQF END
MSKSSGGYTYTETSVLFFHFKVSKDSKSK-MAT........LQF END

Fig. 10

The N-terminal leader sequence is conserved among different species

- Rat MSK<u>N</u>SGGYTYTETSVLFFHFKVPKDSKSK
- Mouse MSK<u>S</u>SGGYTYTETSVLFFHFKV<u>S</u>KDSKSK
- Human M<u>GEP</u>SGGYTYT<u>Q</u>TSI<u>FL</u>FH<u>A</u>KIP<u>FG</u>SKS<u>N</u>

- Cons MSK SGGYTYTETSVLFFHFKVPKDSKSK

Fig. 11

CGCTCTACTT GCTGTAGGAC TCTGGGTG**AT** **G**GGAGAAGAG CGGGAGGGCA GTTCTTTAAC CGTG**TAA**GAG GAGGGACCAT

CCCTTTTGGG GTTCATCAAG **ATG**AGTAAGA ACTCAGGCGG CTACACATAT ACGGAGACCT CAGTATTATT TTTCCATTTC
***

AAGGTCCCAA AAGATTCAAA GTCCAAG**ATG** GCAGCCCTCA AGGACCAGCT GATTGTGAAT CTTCTTAAGG AAGAACAGGT
$$$

CCCCCAGAAC AAGATTACAG TTGTTGGGGT TGGTGCTGTT GGCATGGCTT GTGCCATCA G TATCTTAATG AAGGACTTGG
CTGATGAGCT TGCCCTTGTT GATGTCATAG AAGATAAGCT AAAGGGAGAG ATGATGGAT C TTCAGCATGG CAGCCTTTTC
CTTAAGACAC CAAAAATTGT CTCCAGCAAA GATTATAGTG TGACTGCAAA CTCCAAGCT G GTCATTATCA CCGCGGGGGC
CCGTCAGCAA GAGGGAGAGA GCCGGCTCAA TTTGGTCCAG CGAAACGTGA ACATCTTCA A GTTCATCATT CCAAATGTTG
TGAAATACAG TCCACAGTGC AAACTGCTCA TCGTCTCAAA CCCAGTGGAT ATCTTGACC T ACGTGGCTTG GAAGATCAGC
GGCTTCCCCA AAAACAAAGT TATTGGAAGT GGTTGCAATC TGGATTCGGC TCGGTTCCG T TACCTGATGG GAGAAAGGCT
GGGAGTTCAT CCACTGAGCT GTCACGGGTG GGTCCTGGGA GAGCATGGCG ACTCCAGTG T GCCTGTGTGG AGTGGTGTGA
ACGTCGCCGG CGTCTCCCTG AAGTCTCTGA ACCCGCAGCT GGGCACGGAT GCAGACAAG G AGCAGTGGAA GGATGTGCAC
AAGCAGGTGG TTGACAGTGC ATACGAAGTG ATCAAGCTGA AAGGTTACAC ATCCTGGGC C ATTGGCCTCT CCGTGGCAGA
CTTGGCCGAG AGCATAATGA AGAACCTTAG GCGGGTGCAT CCCATTTCCA CCATGATTA A GGGTCTCTAT GGGATCAAGG
AGGATGTCTT CCTCAGCGTC CCATGTATCC TGGGACAAAA TGGAATCTCA GATGTTGTG A AGGTGACACT GACTCCTGAC
GAGGAGGCCC GCCTGAAGAA GAGTGCAGAT ACCCTCTGGG GAATCCAGAA GGAGCTGCA G TTC**TAA**AGTC TTCCCAGTGT
CCTAGCACTT CACTGTCCAG GCTGCAGCAG GGTTTCTATG GAGACCACGC ACTTCTCATC TGA GCTGTGG TTAGTCCAGT
TGGTCCA

•* Mitochondrial start site
•$ cytosolic start site
•Overlined 5'ORF
•Primer sequences are underlined

Fig. 12A

MSKNSGGYTYTETSVLFFHFKVPKDSKSKMAALKDQLIVNLLKEEQVPQNKITVVGVGAVGMACA
ISILMKDLADELALVDVIEDKLKGEMMDLQHGSLFLKTPKIVSSKDYSVTANSKLVIITAGARQQ
EGESRLNLVQRNVNIFKFIIPNVVKYSPQCKLLIVSNPVDILTYVAWKISGFPKNRVIGSGCNLD
SARFRYLMGERLGVHPLSCHGWVLGEHGDSSVPVWSGVNVAGVSLKSLNPQLGTDADKEQWKDVH
KQVVDSAYEVIKLKGYTSWAIGLSVADLAESIMKNLRRVHPISTMIKGLYGIKEDVFLSVPCILG
QNGISDVVKVTLTPDEEARLKKSADTLWGIQKELQF

Fig. 12B

GAGCAACTTGGCGCTCTACTTGCTGTAGGGCTCTGGGTGATGGGAGAAGAGCGGGAGGGCAGCT TTCTAACCATATAAGAGGAGATA
CCATCCCCTTTTGGTTCATCAAG**ATG**AGTAAGTCCTCAGGCGGCTACACGTACACGGAGACCTCGGTATTATTTTTCCATTTCAAGG
TCTCAAAAGATTCAAAGTCCAAGATGGCAACCCTCAAGGACCAGCTGATTGTGAATCTTCTTAA GGAAGAGCAGGCTCCCCAGAACA
AGATTACAGTTGTTGGGGTTGGTGCTGTTGGCATGGCTTGTGCCATCAGTATCTTAATGAAGGA CTTGGCGGATGAGCTTGCCCTTG
TTGACGTCATGGAAGACAAACTCAAGGGCGAGATGATGGATCTCCAGCATGGCAGCCTCTTCCT TAAAACACCAAAAATTGTCTCCA
GCAAAGACTACTGTGTAACTGCGAACTCCAAGCTGGTCATTATCACCGCGGGGGCCCGTCAGCA AGAGGGGGAGAGCCGGCTCAACC
TGGTCCAGCGAAACGTGAACATCTTCAAGTTCATCATTCCCAACATTGTCAAGTACAGTCCACA CTGCAAGCTGCTGATCGTCTCCA
ATCCAGTGGATATCTTGACCTACGTGGCTTGGAAAATCAGTGGCTTTCCCAAAAACCGAGTAAT TGGAAGTGGTTGCAATCTGGATT
CAGCGCGGTTCCGTTACCTGATGGGAGAGAGGCTGGGGGTTCACGCGCTGAGCTGTCACGGCTG GGTCCTGGGAGAACATGGCGACT
CCAGTGTGCCTGTGTGGAGTGGTGTGAATGTTGCCGGCGTCTCCCTGAAGTCTCTTAACCCAGA ACTGGGCACTGACGCAGACAAGG
AGCAGTGGAAGGAGGTTCACAAGCAGGTGGTGGACAGTGCCTACGAGGTGATCAAGCTGAAAGG TTACACATCCTGGGCCATTGGCC
TCTCTGTGGCAGACTTGGCTGAGAGCATAATGAAGAACCTTAGGCGGGTGCATCCCATTTCCAC CATGATTAAGGGTCTCTATGGAA
TCAATGAGGATGTCTTCCTCAGTGTCCCATGTATCCTGGGACAAAATGGAATCTCGGATGTTGT GAAGGTGACACTGACTCCTGAGG
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TTCACTGTCCAGGCTGCAGCAGGGCTTCTAGGCAGACCACACCCTTCTCGTCTGAGCTGTGGTT AGTACAGTGGTGTTGAGATGGTG
TGGGGAAACATCTCACTCCCCACAGCTCTGCCCTGCTGCCAAGTGGTACTTGTGTAGTGGTGAC CTGGTTAGTGTGACAGTCCCACT
GTCTCTGAGACACACTGCCAACTGCAGGCTTCGATTACCCCTGTGAGCCTGCTGCATTGCTGCC CTGCACCAAACAGCCTAGGCCGA
CGAGTTCCCAGTTAAGTCGTATAACCTGGCTCCAGTGTGTACGTCCATGATGCATATCTTGTGC ATAAATGTTGTACAGGATATTTT
ATATATTATATGTGTCTGTAGTGTGCATTGCAATATTATGTGAGATGTAAGATCTGCATATGGA TGATGGAACCAACCACCCAAGTG
TCATGCCAAATAAAACCTTGAACAGTG

Fig. 12C

MSKSSGGYTYTETSVLFFHFKVSKDSKSKMATLKDQLIVNLLKEEQAPQNKITVVGVGAVGMACA
ISILMKDLADELALVDVMEDKLKGEMMDLQHGSLFLKTPKIVSSKDYCVTANSKLVIITAGARQQ
EGESRLNLVQRNVNIFKFIIPNIVKYSPHCKLLIVSNPVDILTYVAWKISGFPKNRVIGSGCNLD
SARFRYLMGERLGVHALSCHGWVLGEHGDSSVPVWSGVNVAGVSLKSLNPELGTDADKEQWKEVH
KQVVDSAYEVIKLKGYTSWAIGLSVADLAESIMKNLRRVHPISTMIKGLYGINEDVFLSVPCILG
QNGISDVVKVTLTPEEEARLKKSADTLWGIQKELQF

Fig. 12D

CTCTGGTGTTTACTTGAGAAGCCCTGGCTGTGTCCTTGCTGTAGGAGCCGGAGTAGCTCAGAGT GATCTTGTCTGAGGAAAGGCCAG
CCCCACTTGGTTAATAAACCGCGATGGGTGAACCCTCAGGAGGCTATACTTACACCCAAACGTC GATATTCCTTTTCCACGCTAAGA
TTCCTTTTGGTTCCAAGTCCAATATGGCAACTCTAAAGGATCAGCTGATTTATAATCTTCTAAA GGAAGAACAGACCCCCCAGAATA
AGATTACAGTTGTTGGGGTTGGTGCTGTTGGCATGGCCTGTGCCATCAGTATCTTAATGAAGGA CTTGGCAGATGAACTTGCTCTTG
TTGATGTCATCGAAGACAAATTGAAGGGAGAGATGATGGATCTCCAACATGGCAGCCTTTTCCT TAGAACACCAAAGATTGTCTCTG
GCAAAGACTATAATGTAACTGCAAACTCCAAGCTGGTCATTATCACGGCTGGGGCACGTCAGCA AGAGGGAGAAAGCCGTCTTAATT
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ATCCAGTGGATATCTTGACCTACGTGGCTTGGAAGATAAGTGGTTTTCCCAAAAACCGTGTTAT TGGAAGTGGTTGCAATCTGGATT
CAGCCCGATTCCGTTACCTGATGGGGGAAAGGCTGGGAGTTCACCCATTAAGCTGTCATGGGTG GGTCCTTGGGGAACATGGAGATT
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AACAGTGGAAAGAGGTTCACAAGCAGGTGGTTGAGAGTGCTTATGAGGTGATCAAACTCAAAGG CTACACATCCTGGGCTATTGGAC
TCTCTGTAGCAGATTTGGCAGAGAGTATAATGAAGAATCTTAGGCGGGTGCACCCAGTTTCCAC CATGATTAAGGGTCTTTACGGAA
TAAAGGATGATGTCTTCCTTAGTGTTCCTTGCATTTTGGGACAGAATGGAATCTCAGACCTTGT GAAGGTGACTCTGACTTCTGAGG
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TCACTGTCTAGGCTACAACAGGATTCTAGGTGGAGGTTGTGCATGTTGTCCTTTTTATCTGATC TGTGATTAAAGCAGTAATATTTT
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ATTAATCTTGTGTAGTCTTCAACTGGTTAGTGTGAAATAGTTCTGCCACCTCTGACGCACCACT GCCAATGCTGTACGTACTGCATT
TGCCCCTTGAGCCAGGTGGATGTTTACCGTGTGTTATATAACTTCCTGGCTCCTTCACTGAACA TGCCTAGTCCAACATTTTTTCCC
AGTGAGTCACATCCTGGGATCCAGTGTATAAATCCAATATCATGTCTTGTGCATAATTCTTCCA AAGGATCTTATTTTGTGAACTAT
ATCAGTAGTGTACATTACCATATAATGTAAAAAGATCTACATACAAACAATGCAACCAACTATC CAAGTGTTATACCAACTAAAACC
CCCAATAAACCTTGAACAGTG

Fig. 12E

MGEPSGGYTYTQTSIFLFHAKIPFGSKSNMATLKDQLIYNLLKEEQTPQNKITVVGVGAVGMACA
ISILMKDLADELALVDVIEDKLKGEMMDLQHGSLFLRTPKIVSGKDYNVTANSKLVIITAGARQQ
EGESRLNLVQRNVNIFKFIIPNVVKYSPNCKLLIVSNPVDILTYVAWKISGFPKNRVIGSGCNLD
SARFRYLMGERLGVHPLSCHGWVLGEHGDSSVPVWSGMNVAGVSLKTLHPDLGTDKDKEQWKEVH
KQVVESAYEVIKLKGYTSWAIGLSVADLAESIMKNLRRVHPVSTMIKGLYGIKDDVFLSVPCILG
QNGISDLVKVTLTSEEEARLKKSADTLWGIQKELQF

Fig. 12F

```
ClustalW (v1.4) multiple sequence alignment

3 Sequences Aligned           Alignment Score = 26102
Gaps Inserted = 78            Conserved Identities = 1013

Pairwise Alignment Mode: Slow
Pairwise Alignment Parameters:
    Open Gap Penalty = 10.0   Extend Gap Penalty = 5.0

Multiple Alignment Parameters:
    Open Gap Penalty = 0.0    Extend Gap Penalty = 5.0
    Delay Divergent = 40%     Transitions: Weighted

Processing time: 8.7 seconds


ratmitLDHcloned      1            CGCTC-TACTTGCTGT-AGGA-CTCTGG--GTGA--TGG   32
humanmitLDHmRNA      1            CTCTGGTGTTTACT-TGAGAAGCCCTGGCTGTGTCCTTG   38
mousemitLDHmRNA      1 GAGCAACTTGGCGCTC-TACTTGCTGT-AGGG-CTCTGG--GTGA--TGG   43
                                  * **  *  ** ** * **   * ****  ***   * *

ratmitLDHcloned     33 GAG-AAGAGCGGGAGGGCAGTTCTT--TAACCGTGTAAGAGGAGGGACCA   79
humanmitLDHmRNA     39 CTGTAGGAGCCGGA--GTAGCTCAGAGTGATCTTGTCTGAGGAAAGGCCA   86
mousemitLDHmRNA     44 GAG-AAGAGCGGGAGGGCAGCTTTC--TAACCATATAAGAGGAGATACCA   90
                         * * **** ***  * ** *     * * * * *  *****    ***

ratmitLDHcloned     80 TCCCT-TTTGG--GGTTCATCAAGATGAGTAAGAACTCAGGCGGCTACAC  126
humanmitLDHmRNA     87 GCCCCACTTGGTTAATAAACCGCGATGGGTGAACCCTCAGGAGGCTATAC  136
mousemitLDHmRNA     91 TCCCC-TTTTG--G-TTCATCAAGATGAGTAAGTCCTCAGGCGGCTACAC  136
                        ***   ** *    *  * *  **** ** *   ****** ***** **

ratmitLDHcloned    127 ATATACGGAGACCTCAGTATTATTTTTCCATTTCAAGGTCCCAAAAGATT  176
humanmitLDHmRNA    137 TTACACCCAAACGTCGATATTCCTTTTCCACGCTAAGATTCCTTTTGGTT  186
mousemitLDHmRNA    137 GTACACGGAGACCTCGGTATTATTTTTCCATTTCAAGGTCTCAAAAGATT  186
                        ** **  * ** **  ****  *******    *** *  *    * **

ratmitLDHcloned    177 CAAAGTCCAAGATGGCAGCCCTCAAGGACCAGCTGATT-GTGAATCTTCT  225
humanmitLDHmRNA    187 CCAAGTCCAATATGGCAACTCTAAAGGATCAGCTGATTTAT-AATCTTCT  235
mousemitLDHmRNA    187 CAAAGTCCAAGATGGCAACCCTCAAGGACCAGCTGATT-GTGAATCTTCT  235
                       * ******** ****** * ** ***** *********  * ********

ratmitLDHcloned    226 TAAGGAAGAACAGGTCCCCCAGAACAAGATTACAGTTGTTGGGGTTGGTG  275
humanmitLDHmRNA    236 AAAGGAAGAACAGACCCCCCAGAATAAGATTACAGTTGTTGGGGTTGGTG  285
mousemitLDHmRNA    236 TAAGGAAGAGCAGGCTCCCCAGAACAAGATTACAGTTGTTGGGGTTGGTG  285
                        ******** ***   ******** *************************

ratmitLDHcloned    276 CTGTTGGCATGGCTTGTGCCATCAGTATCTTAATGAAGGACTTGGCTGAT  325
humanmitLDHmRNA    286 CTGTTGGCATGGCCTGTGCCATCAGTATCTTAATGAAGGACTTGGCAGAT  335
mousemitLDHmRNA    286 CTGTTGGCATGGCTTGTGCCATCAGTATCTTAATGAAGGACTTGGCGGAT  335
                       ************* ******************************** ***
```

Fig. 13A

```
ratmitLDHcloned    326 GAGCTTGCCCTTGTTGATGTCATAGAAGATAAGCTAAAGGGAGAGATGAT  375
humanmitLDHmRNA    336 GAACTTGCTCTTGTTGATGTCATCGAAGACAAATTGAAGGGAGAGATGAT  385
mousemitLDHmRNA    336 GAGCTTGCCCTTGTTGACGTCATGGAAGACAAACTCAAGGGCGAGATGAT  385
                       ** ***** ******** ***** ***** **   * ***** ********

ratmitLDHcloned    376 GGATCTTCAGCATGGCAGCCTTTTCCTTAAGACACCAAAAATTGTCTCCA  425
humanmitLDHmRNA    386 GGATCTCCAACATGGCAGCCTTTTCCTTAGAACACCAAAGATTGTCTCTG  435
mousemitLDHmRNA    386 GGATCTCCAGCATGGCAGCCTCTTCCTTAAAACACCAAAAATTGTCTCCA  435
                       ****** ** *********** *******  ******** ********

ratmitLDHcloned    426 GCAAAGATTATAGTGTGACTGCAAACTCCAAGCTGGTCATTATCACCGCG  475
humanmitLDHmRNA    436 GCAAAGACTATAATGTAACTGCAAACTCCAAGCTGGTCATTATCACGGCT  485
mousemitLDHmRNA    436 GCAAAGACTACTGTGTAACTGCGAACTCCAAGCTGGTCATTATCACCGCG  485
                       ******* **    *** ***** *********************** **

ratmitLDHcloned    476 GGGGCCCGTCAGCAAGAGGGAGAGAGCCGGCTCAATTTGGTCCAGCGAAA  525
humanmitLDHmRNA    486 GGGGCACGTCAGCAAGAGGGAGAAAGCCGTCTTAATTTGGTCCAGCGTAA  535
mousemitLDHmRNA    486 GGGGCCCGTCAGCAAGAGGGGGAGAGCCGGCTCAACCTGGTCCAGCGAAA  535
                       ***** ************** ** ***** ** **  ********** **

ratmitLDHcloned    526 CGTGAACATCTTCAAGTTCATCATTCCAAATGTTGTGAAATACAGTCCAC  575
humanmitLDHmRNA    536 CGTGAACATATTTAAATTCATCATTCCTAATGTTGTAAAATACAGCCCGA  585
mousemitLDHmRNA    536 CGTGAACATCTTCAAGTTCATCATTCCCAACATTGTCAAGTACAGTCCAC  585
                       ********* ** ** *********** **  **** ** ***** **

ratmitLDHcloned    576 AGTGCAAACTGCTCATCGTCTCAAACCCAGTGGATATCTTGACCTACGTG  625
humanmitLDHmRNA    586 ACTGCAAGTTGCTTATTGTTTCAAATCCAGTGGATATCTTGACCTACGTG  635
mousemitLDHmRNA    586 ACTGCAAGCTGCTGATCGTCTCCAATCCAGTGGATATCTTGACCTACGTG  635
                       * *****  **** ** ** ** ** ***********************

ratmitLDHcloned    626 GCTTGGAAGATCAGCGGCTTCCCCAAAAACAAAGTTATTGGAAGTGGTTG  675
humanmitLDHmRNA    636 GCTTGGAAGATAAGTGGTTTTCCCAAAAACCGTGTTATTGGAAGTGGTTG  685
mousemitLDHmRNA    636 GCTTGGAAAATCAGTGGCTTTCCCAAAAACCGAGTAATTGGAAGTGGTTG  685
                       ******** ** ** ** ** *********    ** **************

ratmitLDHcloned    676 CAATCTGGATTCGGCTCGGTTCCGTTACCTGATGGGAGAAAGGCTGGGAG  725
humanmitLDHmRNA    686 CAATCTGGATTCAGCCCGATTCCGTTACCTGATGGGGGAAAGGCTGGGAG  735
mousemitLDHmRNA    686 CAATCTGGATTCAGCGCGGTTCCGTTACCTGATGGGAGAGAGGCTGGGGG  735
                       ************ ** ** ***************** ** ******** *

ratmitLDHcloned    726 TTCATCCACTGAGCTGTCACGGGTGGGTCCTGGGAGAGCATGGCGACTCC  775
humanmitLDHmRNA    736 TTCACCCATTAAGCTGTCATGGGTGGGTCCTTGGGGAACATGGAGATTCC  785
mousemitLDHmRNA    736 TTCACGCGCTGAGCTGTCACGGCTGGGTCCTGGGAGAACATGGCGACTCC  785
                       ****  *  * ******** ** ******** ** ** ***** ** ***

ratmitLDHcloned    776 AGTGTGCCTGTGTGGAGTGGTGTGAACGTCGCCGGCGTCTCCCTGAAGTC  825
humanmitLDHmRNA    786 AGTGTGCCTGTATGGAGTGGAATGAATGTTGCTGGTGTCTCTCTGAAGAC  835
mousemitLDHmRNA    786 AGTGTGCCTGTGTGGAGTGGTGTGAATGTTGCCGGCGTCTCCCTGAAGTC  835
                       *********** ********  **** ** ** ** ***** ****** *
```

Fig. 13B

```
ratmitLDHcloned  826 TCTGAACCCGCAGCTGGGCACGGATGCAGACAAGGAGCAGTGGAAGGATG  875
humanmitLDHmRNA  836 TCTGCACCCAGATTTAGGGACTGATAAAGATAAGGAACAGTGGAAAGAGG  885
mousemitLDHmRNA  836 TCTTAACCCAGAACTGGGCACTGACGCAGACAAGGAGCAGTGGAAGGAGG  885
                     ***  **** *   * ** ** **   *** ***** ******** ** *

ratmitLDHcloned  876 TGCACAAGCAGGTGGTTGACAGTGCATACGAAGTGATCAAGCTGAAAGGT  925
humanmitLDHmRNA  886 TTCACAAGCAGGTGGTTGAGAGTGCTTATGAGGTGATCAAACTCAAAGGC  935
mousemitLDHmRNA  886 TTCACAAGCAGGTGGTGGACAGTGCCTACGAGGTGATCAAGCTGAAAGGT  935
                     * ************** ** ***** ** ** ******** ** *****

ratmitLDHcloned  926 TACACATCCTGGGCCATTGGCCTCTCCGTGGCAGACTTGGCCGAGAGCAT  975
humanmitLDHmRNA  936 TACACATCCTGGGCTATTGGACTCTCTGTAGCAGATTTGGCAGAGAGTAT  985
mousemitLDHmRNA  936 TACACATCCTGGGCCATTGGCCTCTCTGTGGCAGACTTGGCTGAGAGCAT  985
                     ************** ***** ***** ** ***** ***** ***** **

ratmitLDHcloned  976 AATGAAGAACCTTAGGCGGGTGCATCCCA-TTTCCACCATGATTAAGGGT 1024
humanmitLDHmRNA  986 AATGAAGAATCTTAGGCGGGTGCA-CCCAGTTTCCACCATGATTAAGGGT 1034
mousemitLDHmRNA  986 AATGAAGAACCTTAGGCGGGTGCATCCCA-TTTCCACCATGATTAAGGGT 1034
                     ********* ************** **** *******************

ratmitLDHcloned 1025 CTCTATGGGATCAAGGAGGATGTCTTCCTCAGCGTCCCATGTATCCTGGG 1074
humanmitLDHmRNA 1035 CTTTACGGAATAAAGGATGATGTCTTCCTTAGTGTTCCTTGCATTTTGGG 1084
mousemitLDHmRNA 1035 CTCTATGGAATCAATGAGGATGTCTTCCTCAGTGTCCCATGTATCCTGGG 1084
                     ** ** ** ** ** ** *********** ** ** ** ** **  ****

ratmitLDHcloned 1075 ACAAAATGGAATCTCAGATGTTGTGAAGGTGACACTGACTCCTGACGAGG 1124
humanmitLDHmRNA 1085 ACAGAATGGAATCTCAGACCTTGTGAAGGTGACTCTGACTTCTGAGGAAG 1134
mousemitLDHmRNA 1085 ACAAAATGGAATCTCGGATGTTGTGAAGGTGACACTGACTCCTGAGGAAG 1134
                     *** *********** **  ************* ****** **** ** *

ratmitLDHcloned 1125 AGGCCCGCCTGAAGAAGAGTGCAGATACCCTCTGGGGAATCCAGAAGGAG 1174
humanmitLDHmRNA 1135 AGGCCCGTTTGAAGAAGAGTGCAGATACACTTTGGGGGATCCAAAAGGAG 1184
mousemitLDHmRNA 1135 AGGCCCGCCTGAAGAAGAGCGCAGACACCCTCTGGGGAATCCAGAAGGAG 1184
                     *******  ********** ***** ** ** ***** ***** ******

ratmitLDHcloned 1175 CTGCAGTTCTAAAGTCTTCCCAGTGTCCTAGCACTTCACTGTCCAGGCTG 1224
humanmitLDHmRNA 1185 CTGCAATTTTAAAGTCTTCT-GATGTCATATCATTTCACTGTCTAGGCTA 1233
mousemitLDHmRNA 1185 CTGCAGTTCTAAAGTCTTCCCCGTGTCCTAGCACTTCACTGTCCAGGCTG 1234
                     ***** ** **********    **** ** ** ********* *****

ratmitLDHcloned 1225 CAGCAGGGTTTCTA--TGG-AGACCACGCAC-TT--C-TC---ATCTGAG 1264
humanmitLDHmRNA 1234 CAACAGGATT-CTAGGTGG-AGGTTGTGCATGTTGTCCTTTTTATCTGAT 1281
mousemitLDHmRNA 1235 CAGCAGGGCTTCTA---GGCAGACCACACCC-TT--C-TC---GTCTGAG 1274
                     ** **** * ***    ** **        *   **  * *    *****

ratmitLDHcloned 1265 CTGTGGTTAGTCCAGTTG-GTCCAAAG                        1290
humanmitLDHmRNA 1282 CTGTGATTAAAGCAGTAATATTTTAAGATGGACTGGAAAAACATCAACT 1331
mousemitLDHmRNA 1275 CTGTGGTTAGTACAGT-G-GTGTTGAGATGGTGTGGGGAAA-CAT---CT 1318
                     ***** ***   ****   *    **
```

Fig. 13C

```
ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1332 CCTGAAGTTAGAAATAAGAATGGTTTGTAAAATCCACAGCTATATCCTGA 1381
mousemitLDHmRNA 1319 C---A--CT-----C-----------------CCCACAGCTCTGCCCTGC 1341

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1382 TGCTGGATGGTATTAATCTTGTGTAGTCTTCAACTGGTTAGTGTGAAATA 1431
mousemitLDHmRNA 1342 TGCCAAGTGG---TA--CTTGTGTAGTGGTGACCTGGTTAGTGTGA--CA 1384

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1432 GTTCTGCCACCTCTGACGCACCACTGCCAATGCTGTACGTACTGCATTTG 1481
mousemitLDHmRNA 1385 GTCCCACTGTCTCTGAGACAC-ACTGCCAA--CTGCA-G-GCTTCGATTA 1429

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1482 CCCCTTGAGCCAGGTGGATGTTTACCGTGTGTTATATAACTTCCTGGCTC 1531
mousemitLDHmRNA 1430 CCCCT-------G-TG-A-G----CC-TG--CTG--C-A-TTGCTG-C-C 1456

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1532 CTTCACTGAACATGCCTAGTCCAACATTTTTTCCCAGT-GAGTCACATC- 1579
mousemitLDHmRNA 1457 CTGCACCAAACA-GCCTAGGCCGACGAGTT--CCCAGTTAAGTCGTATAA 1503

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1580 CTGGGATCCAGTGTATAAATCCAATAT-CATGTCTTGTGCATAATTCTTC 1628
mousemitLDHmRNA 1504 CCTGGCTCCAGTGTGTACGTCCATGATGCATATCTTGTGCATAAATGTTG 1553

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1629 CAAAGGATCTTATTT-TGTGAACTATATCAGTAGTGTACATTACCATATA 1677
mousemitLDHmRNA 1554 TACAGGATATTTTATATATTATATGTGTCTGTAGTGTGCATTGCAATATT 1603

ratmitLDHcloned 1291                                                    1290
humanmitLDHmRNA 1678 ATGTAA-A---AAGATCTACATACAAACAATGCAACCAACTATCCAAGTG 1723
mousemitLDHmRNA 1604 ATGTGAGATGTAAGATCTGCATATGGATGATGGAACCAACCACCCAAGTG 1653

ratmitLDHcloned 1291                                      1290
humanmitLDHmRNA 1724 TTATACCAACTAAAACCCCCAATAA-ACCTTGAACAGTG 1761
mousemitLDHmRNA 1654 TCATGCCAAATAAAACCTTGAACAGTG             1680
```

Fig. 13D

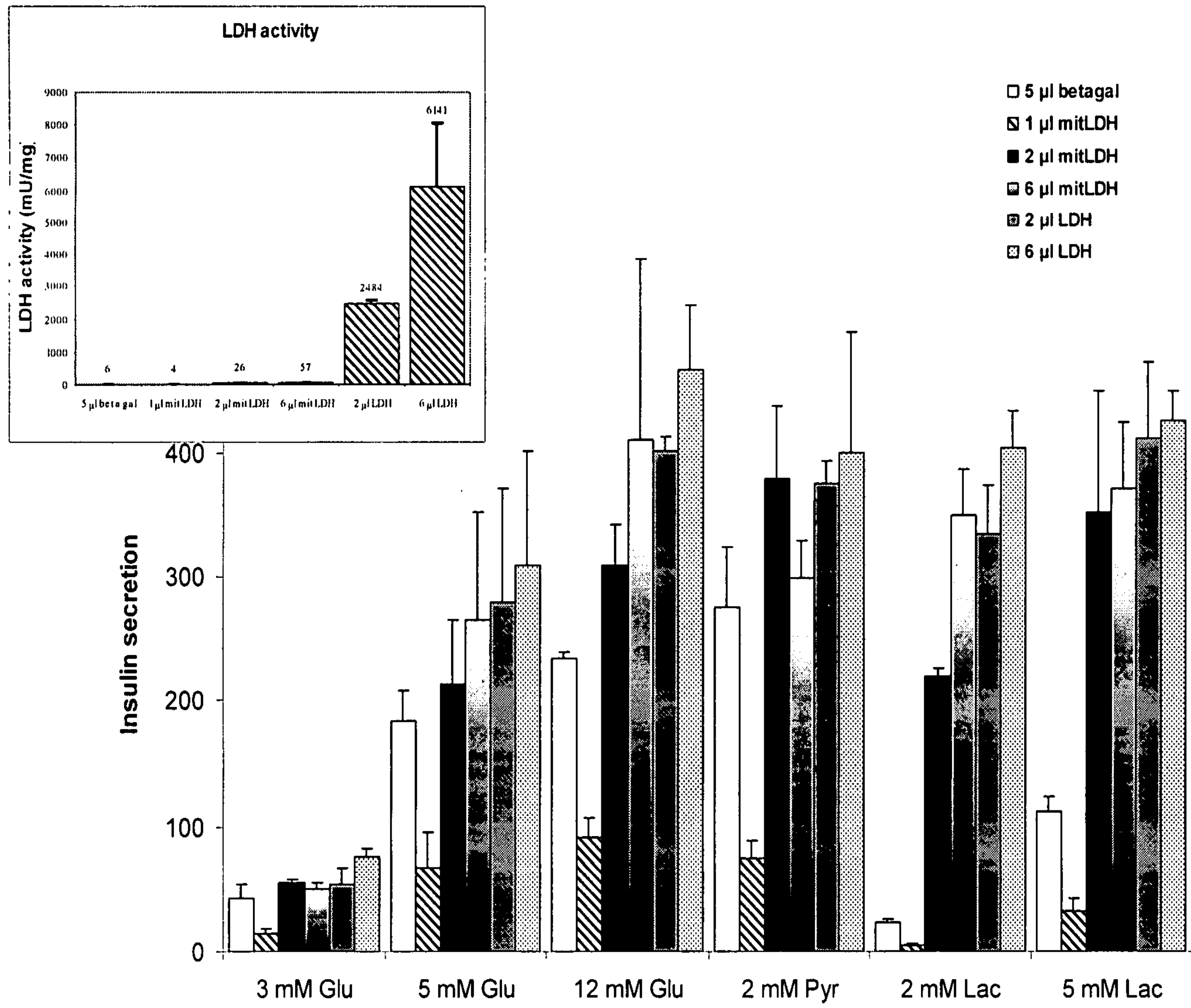
LDH activity
LDH activity (mU/mg)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
6
4
26
57
2484
6141
5 µl betagal
1 µl mitLDH
2 µl mitLDH
6 µl mitLDH
2 µl LDH
6 µl LDH
5 µl betagal
1 µl mitLDH
2 µl mitLDH
6 µl mitLDH
2 µl LDH
6 µl LDH
Insulin secretion
400
300
200
100
0
3 mM Glu
5 mM Glu
12 mM Glu
2 mM Pyr
2 mM Lac
5 mM Lac

Fig. 14